EXHIBIT C

NDA 213005

TENTATIVE APPROVAL

Liquidia Technologies, Inc.
Attention: Jennifer Weidman
VP Regulatory Affairs
419 Davis Dr., Suite 100
PO Box 110085
Research Triangle Park, NC 17709

Dear Ms. Weidman:

Please refer to your new drug application (NDA) dated and received January 24, 2020, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Yutrepia (treprostinil inhalation powder) Oral Inhalation.

We acknowledge receipt of your amendment dated May 7, 2021, which constituted a complete response to our November 24, 2020, action letter.

This NDA provides for the use of Yutrepia (treprostinil inhalation powder) Oral Inhalation for the treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability in patients with NYHA Functional Class II-III symptoms.

We have completed our review of this application, as amended. It is tentatively approved under 21 CFR 314.105 for use as recommended in the enclosed final labeling (Prescribing Information and Instructions for Use) submitted November 4, 2021, carton and container labeling submitted November 2, 2021. This determination is based upon information available to the Agency at this time, [i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product]. This determination is subject to change on the basis of any new information that may come to our attention.

Final approval of your application is subject to expiration of a period of patent protection and/or exclusivity. Therefore, final approval of your application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be granted before the period has expired.

A listed drug(s) upon which your application relies is subject to a period of patent protection and your application contains a certification(s) to one or more patents under section 505(b)(2)(A)(iv) of the FD&C Act stating that the patent(s) is/are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of, this drug product under this application ("paragraph IV certification").

Section 505(c)(3)(C) of the FD&C Act provides that approval of a new drug application submitted pursuant to section 505(b)(2) of the FD&C Act that includes a paragraph IV certification shall be made effective immediately, unless an action is brought for infringement of one or more of the patents that were the subject of a paragraph IV certification. If such a patent infringement action is brought prior to the expiration of 45 days from the later of the date the notice provided under section 505(b)(3) is received by the patent owner or approved application holder, your application is subject to a 30-month stay of approval, unless other conditions are met. You notified us that you complied with the requirements of section 505(b)(3) of the FD&C Act.

In addition, you have notified the Agency that the patent owner and/or approved application holder has initiated a patent infringement suit against you with respect to patents 9593066, 9604901, and 10716793 in the United States District Court for the District of Delaware, case number 1:20-cv-00755- RGA. Therefore, final approval cannot be granted until:

(1)

- expiration of the 30-month period provided for in section 505(c)(3)(C) beginning on the later of the date of receipt by any owner of the listed patent or application holder of the notice required under section 505(b)(3), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or
- the date the court decides that the patent(s) is/are invalid or not infringed as described in section 505(c)(3)(C)(i), (ii), (iii,) or (iv) of the FD&C Act, or,
- the listed patent(s) has/have expired, and

(2) we are assured there is no new information that would affect whether final approval should be granted.

To obtain final approval of this application, submit an amendment two or six months prior to the: (1) expiration of the patent(s) and/or exclusivity protection or (2) date you believe that your NDA will be eligible for final approval, as appropriate. In your cover letter, clearly identify your amendment as **"REQUEST FOR FINAL APPROVAL"**. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of any relevant court order or judgment settlement, or licensing agreement, as appropriate. In addition to a safety update, the amendment should also identify changes, if any, in the conditions under which your product was tentatively approved, i.e., updated labeling; chemistry, manufacturing, and controls data; and risk evaluation and mitigation strategy (REMS). If there are no changes, clearly state so in your cover letter. Any changes require our review before final approval and the goal date for our review will be set accordingly.

Until we issue a final approval letter, this NDA is not approved.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that if this application is ultimately approved, you will need to meet these requirements.

PMR Descriptions:

- Phase 3 randomized, double-blind, placebo-controlled trial to evaluate the efficacy, safety, and pharmacokinetics of LIQ861 (Treprostinil) in children with WHO Group 1 Pulmonary Arterial Hypertension, aged 7 to 17 years; 16-week trial.

- Phase 3 PK and safety study in PH, open-label, dose escalation study to assess safety, tolerability, and pharmacokinetics of LIQ861 in children with WHO Group 1 Pulmonary Arterial Hypertension, aged 3 to 6 years; 12-week trial.

If you have any questions, please call Maryam Changi, Regulatory Project Manager, at (240) 402-2725.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Instructions for Use
- Carton and Container Labeling

U.S. Food and Drug Administration
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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use YUTREPIA™ safely and effectively. See full prescribing information for YUTREPIA™.

YUTREPIA™ (treprostinil) inhalation powder, for oral inhalation
Initial U.S. Approval: 2002

----------**INDICATIONS AND USAGE**----------
YUTREPIA is a prostacyclin mimetic indicated for the treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability in patients with NYHA Functional Class II-III symptoms. (1)

----------**DOSAGE AND ADMINISTRATION**----------
- For oral inhalation only. Do not swallow YUTREPIA capsules. Use only with the provided inhaler (2)
- YUTREPIA should be administered 3 to 5 times per day. The contents of each capsule can be inhaled in 2 breaths. (2.1)
- See *Dosage and Administration* for full instructions on dosing of patients who are treprostinil-naïve or transitioning from treprostinil inhalation solution to YUTREPIA (2.1)

----------**DOSAGE FORMS AND STRENGTHS**----------
YUTREPIA inhalation powder contained in capsule is available in 4 strengths: 26.5 mcg, 53 mcg, 79.5 mcg, 106 mcg (3)

----------**CONTRAINDICATIONS**----------
None (4)

----------**WARNINGS AND PRECAUTIONS**----------
- Treprostinil may cause symptomatic hypotension. (5.1)
- Treprostinil inhibits platelet aggregation and increases the risk of bleeding. (5.2)
- Dosage adjustments may be necessary if inhibitors or inducers of CYP2C8 are added or withdrawn. (5.3, 7.1)

----------**ADVERSE REACTIONS**----------
Most common adverse reactions with YUTREPIA (≥10%) are cough, headache, throat irritation, and dizziness. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Liquidia Technologies, Inc. at 1-XXX-XXX-XXXX or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling (Instructions for Use).

Revised: 11/2021

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* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

YUTREPIA™ is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability in patients with NYHA Functional Class II-III symptoms.

2 DOSAGE AND ADMINISTRATION

2.1 Usual Dosage In Adults

YUTREPIA capsules are for oral inhalation only and should be used only with the supplied inhaler.

YUTREPIA Dosing in treprostinil-naïve patients:

In patients naïve to treprostinil, therapy should begin with 26.5 mcg 3 to 5 times per day, in 2 breaths based on patient response.

Dosing in patients transitioning from treprostinil inhalation solution (Tyvaso):

Patients transitioning from treprostinil inhalation solution (Tyvaso), can begin YUTREPIA therapy 3 to 5 times per day, in 2 breaths, using the doses specified below (Table 1):

Table 1: YUTREPIA Dosing in Patients Transitioning from Treprostinil Inhalation Solution

Current Tyvaso Dose*	YUTREPIA Dose
Breaths	mcg
≤5	26.5
≥6 and ≤8	53
≥9 and ≤11	79.5
≥12 and ≤14	106
≥15 and ≤17	132.5
≥18	159

*Each breath of Tyvaso delivers approximately 6 mcg of treprostinil

In treprostinil-naïve patients and those transitioning from treprostinil inhalation solution, dose increases of 26.5 mcg per dose each week may be implemented, as tolerated. The target maintenance dosage is 79.5-106 mcg, 4 times daily. Doses above 848 mcg per day have not been studied.

3 DOSAGE FORMS AND STRENGTHS

YUTREPIA inhalation powder contained in capsule available in 4 strengths:

- 26.5 mcg: opaque yellow cap and clear body capsule with “LIQUIDIA 26.5” in black radial imprint on capsule cap.
- 53 mcg: opaque green cap and clear body capsule with “LIQUIDIA 53” in white radial imprint on capsule cap.

- 79.5 mcg: opaque blue cap and clear body capsule with "LIQUIDIA 79.5" in white radial imprint on capsule cap.
- 106 mcg: opaque purple cap and clear body capsule with "LIQUIDIA 106" in white radial imprint on capsule cap.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Symptomatic Hypotension

Treprostinil is a pulmonary and systemic vasodilator. In patients with low systemic arterial pressure, treatment with treprostinil may produce symptomatic hypotension.

5.2 Risk of Bleeding

Treprostinil inhibits platelet aggregation and increases the risk of bleeding.

5.3 Effect of Other Drugs on Treprostinil

Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) may increase exposure (both C_{max} and AUC) to treprostinil. Co-administration of a CYP2C8 enzyme inducer (e.g., rifampin) may decrease exposure to treprostinil. Increased exposure is likely to increase adverse events associated with treprostinil administration, whereas decreased exposure is likely to reduce clinical effectiveness *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

The following potential adverse reactions are described in Warnings and Precautions (5):

- Decrease in systemic blood pressure *[see Warnings and Precautions (5.1)]*.
- Bleeding *[see Warnings and Precautions (5.2)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety and tolerability of YUTREPIA was evaluated in an open label study (INSPIRE) of 121 patients with PAH (WHO Group 1 and NYHA Functional Class II [80 patients] and Class III [41 patients]) followed for up to 2 months. The most commonly reported adverse reactions included cough, headache, throat irritation, dizziness, which are known side effects of treprostinil inhalation solution. Table 2 lists the adverse reactions that occurred at a rate of at least 4% of the overall INSPIRE safety population. The adverse reactions in the INSPIRE study were consistent with those observed in previous studies of inhaled treprostinil.

Table 2: Adverse Reactions Occurring in ≥ 4% of Patients in the INSPIRE Study

Adverse Reaction	Transition* N=55 n (%)	Add-On† N=66 n (%)
Cough	15 (27)	36 (55)
Headache	14 (25)	18 (27)
Throat Irritation	5 (9)	14 (21)
Dizziness	6 (11)	7 (11)
Diarrhea	3 (6)	8 (12)
Chest Discomfort	5 (9)	5 (8)
Nausea	4 (7)	5 (8)
Dyspnea	3 (6)	3 (5)
Flushing	1 (2)	5 (8)
Oropharyngeal Pain	1 (2)	4 (6)

*Transition: Patients were on stable doses of treprostinil inhalation solution for at least 3 months prior to enrollment in the study and transitioned to treatment with YUTREPIA.

†Add-on: Patients were prostacyclin-naïve and were taking no more than 2 approved oral PAH therapies for at least 3 months at time of enrollment and addition of treatment with YUTREPIA.

6.2 Adverse Reactions Identified in Post-Marketing Experience

The following adverse reaction has been identified during the post-approval use of treprostinil inhalation solution. Because this reaction is reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure:

- Angioedema

7 DRUG INTERACTIONS

7.1 Effect of Cytochrome P450 Inhibitors and Inducers

In vitro studies of human hepatic microsomes showed that treprostinil does not inhibit cytochrome P450 (CYP) isoenzymes CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A.

Additionally, treprostinil does not induce cytochrome P450 isoenzymes CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A.

Human pharmacokinetic studies with an oral formulation of treprostinil (treprostinil diolamine) indicated that co-administration of the cytochrome P450 (CYP) 2C8 enzyme inhibitor gemfibrozil increases exposure (both C_{max} and AUC) to treprostinil. Co-administration of the CYP2C8 enzyme inducer rifampin decreases exposure to treprostinil. It is unclear if the safety and efficacy of treprostinil by the inhalation route are altered by inhibitors or inducers of CYP2C8 *[see Warnings and Precautions (5.3)]*.

7.2 Effect of Other Drugs on Treprostinil

Drug interaction studies have been carried out with treprostinil (oral or subcutaneous) co-administered with acetaminophen (4 g/day), warfarin (25 mg/day), and fluconazole (200 mg/day), respectively, in healthy volunteers. These studies did not show a clinically significant effect on the pharmacokinetics of treprostinil. Treprostinil does not affect the pharmacokinetics or pharmacodynamics of warfarin. The pharmacokinetics of R- and S- warfarin and the INR in healthy subjects given a single 25 mg dose of warfarin were unaffected by continuous subcutaneous infusion of treprostinil at an infusion rate of 10 ng/kg/min.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited case reports of treprostinil use in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. However, there are risks to the mother and the fetus associated with pulmonary arterial hypertension (see *Clinical Considerations*). In animal studies, no adverse reproductive and developmental effects were seen for treprostinil at ≥9 and ≥145 times the human exposure when based on C_{max} and AUC, respectively, following a single YUTREPIA dose of 79.5 mcg *[see Clinical Pharmacology (12.3)]*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and embryo-fetal risk

Pulmonary arterial hypertension is associated with an increased risk of maternal and fetal mortality.

Data

Animal reproduction studies have been conducted with treprostinil via continuous subcutaneous administration and with treprostinil diolamine administered orally. In studies with orally administered treprostinil diolamine, no adverse effect doses for fetal viability/growth, fetal development (teratogenicity), and postnatal development were determined in rats. In pregnant rats, no evidence of harm to the fetus was observed following oral administration of treprostinil diolamine at the highest dose tested (20 mg/kg/day), which represents about 154 and 1479 times the human exposure, when based on C_{max} and AUC, respectively, following a single YUTREPIA dose of 79.5 mcg. In pregnant rabbits, external fetal and soft tissue malformations and fetal skeletal malformation occurred. The dose at which no adverse effects were seen (0.5 mg/kg/day) represents about 9 and 145 times the human exposure, when based on C_{max} and AUC, respectively, following a single YUTREPIA dose of 79.5 mcg. No treprostinil treatment-related effects on labor and delivery were seen in animal studies. Animal reproduction studies are not always predictive of human response.

8.2 Lactation

Risk Summary

There are no data on the presence of treprostinil in human milk, the effects on the breastfed infant, or the effects on milk production.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Placebo-controlled clinical studies of treprostinil inhalation solution did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. The open-label INSPIRE study in PAH patients included 28 patients aged 65 and over in which no age-related differences were noted. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of hepatic, renal, or cardiac dysfunction, and of concomitant diseases or other drug therapy.

8.6 Patients with Hepatic Insufficiency

Plasma clearance of treprostinil, delivered subcutaneously, was reduced up to 80% in subjects with mild-to-moderate hepatic insufficiency. Uptitrate slowly when treating patients with hepatic insufficiency because of the risk of an increase in systemic exposure which may lead to an increase in dose-dependent adverse effects. Treprostinil has not been studied in patients with severe hepatic insufficiency *[see Clinical Pharmacology (12.3)]*.

8.7 Patients with Renal Insufficiency

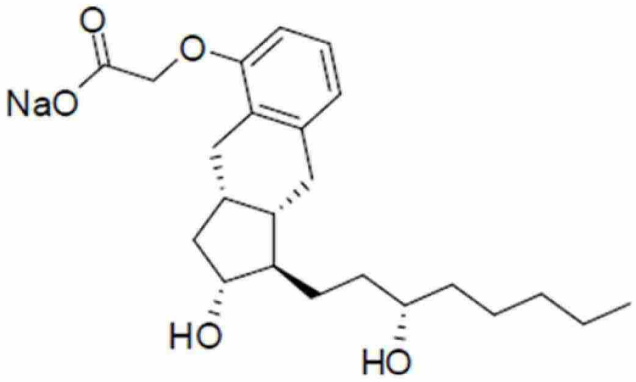
No dose adjustments are required in patients with renal impairment. Treprostinil is not cleared by dialysis *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

In general, symptoms of overdose with treprostinil include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Provide general supportive care until the symptoms of overdose have resolved.

11 DESCRIPTION

YUTREPIA contains treprostinil sodium, a prostacyclin vasodilator. The chemical name for tresprostinil sodium is 2-{[(1R,2R,3aS,9aS)-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H,2H,3H,3aH,4H,9H,9aH-cyclopenta[b]naphthalen-5-yl]oxy}acetic acid, sodium salt with the structural formula:



Treprostinil sodium has a molecular formula of $C_{23}H_{33}O_5Na$ and a molecular weight of 412.49 daltons equivalent to 390.5 daltons of Treprostinil

YUTREPIA inhalation powder contained in a capsule is intended for oral inhalation. The capsule contains white to off-white powder of treprostinil sodium and the inactive ingredients trehalose, polysorbate 80, L-leucine, sodium citrate, and sodium chloride. 26.5 mcg of treprostinil is equivalent to 28 mcg of treprostinil sodium.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation.

12.2 Pharmacodynamics

In animals, the vasodilatory effects reduce right and left ventricular afterload and increase cardiac output and stroke volume. Other studies have shown that treprostinil causes a dose-related negative inotropic and lusitropic effect. No major effects on cardiac conduction have been observed. Treprostinil produces vasodilation and tachycardia.

Cardiac Electrophysiology

In a clinical trial of 240 healthy volunteers, single doses of treprostinil inhalation solution 54 mcg (the target maintenance dose per session) and 84 mcg (supratherapeutic inhalation dose) prolonged the corrected QTc interval by approximately 10 ms. The QTc effect dissipated rapidly as the concentration of treprostinil decreased.

12.3 Pharmacokinetics

Absorption

in healthy volunteer studies, the systemic exposure (AUC and C_{max}) post-inhalation was shown to be proportional to the YUTREPIA doses administered (25 mcg – 150 mcg). The treprostinil mean C_{max}, mean AUC_{inf} and median T_{max} following a single inhaled target maintenance dose of 79.5 mcg YUTREPIA were 1.48 ng/mL, 1.04 hr.ng/mL and 0.13 hr, respectively.

Distribution

In vitro treprostinil is 91% bound to human plasma proteins over the 330-10,000 ng/mL concentration range.

Metabolism and Excretion

Of subcutaneously administered treprostinil, only 4% is excreted unchanged in urine. Treprostinil is substantially metabolized by the liver, primarily by CYP2C8. Metabolites are excreted in urine (79%) and feces (13%) over 10 days. Five apparently inactive metabolites were detected in the urine, each accounting for 10-15% of the dose administered. Four of the metabolites are products of oxidation of the 3-hydroxyloctyl side chain and one is a glucuroconjugated derivative (treprostinil glucuronide).

Elimination

Following inhaled administration of YUTREPIA, disposition and elimination is monophasic with a half-life of approximately 30 minutes.

Specific Populations

Hepatic Insufficiency

Plasma clearance of treprostinil, delivered subcutaneously, was reduced up to 80% in subjects presenting with mild-to-moderate hepatic insufficiency. Treprostinil has not been studied in patients with severe hepatic insufficiency *[see Use in Specific Populations (8.6)]*.

Renal Insufficiency

In patients with severe renal impairment requiring dialysis (n=8), administration of a single 1 mg dose of orally administered treprostinil pre-and post-dialysis resulted in AUC0-inf that was not significantly altered compared to healthy subjects *[see Use in Specific Populations (8.7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

A two-year rat carcinogenicity study was performed with treprostinil inhalation solution at target treprostinil doses of 5.26, 10.6, and 34.1 µg/kg/day. There was no evidence for carcinogenic potential associated with treprostinil inhalation in rats at systemic exposure levels up to 35 times following a single YUTREPIA dose of 79.5 mcg *[see Clinical Pharmacology (12.3)]*. *In vitro* and *in vivo* genetic toxicology studies did not demonstrate any mutagenic or clastogenic effects of treprostinil. Treprostinil sodium did not affect fertility or mating performance of male or female rats given continuous subcutaneous (sc) infusions at rates of up to 450 ng treprostinil/kg/min. In this study, males were dosed from 10 weeks prior to mating and through the 2-week mating period. Females were dosed from 2 weeks prior to mating until gestational day 6.

Oral administration of treprostinil diolamine to Tg.rasH2 mice at 0, 5, 10 and 20 mg/kg/day in males and 0, 3, 7.5 and 15 mg/kg/day in females daily for 26 weeks did not significantly increase the incidence of tumors.

Treprostinil diolamine was tested *in vivo* in a rat micronucleus assay and did not induce an increased incidence of micronucleated polychromatic erythrocytes.

13.2 Animal Toxicology and/or Pharmacology

In a 2-year rat study with treprostinil inhalation at target doses of 5.26, 10.6, and 34.1 mcg/kg/day, there were more deaths (11) in the mid- and high-dose treprostinil groups during the first 9 weeks of the study, compared to 1 in control groups. At the high-dose level, males showed a higher incidence of inflammation in teeth and preputial gland, and females showed high incidences of inflammation and urothelial hyperplasia in the urinary bladder. The exposures in rats at mid- and high-dose levels were about 15 and 35 times, respectively, the clinical exposure following a single YUTREPIA dose of 79.5 mcg *[see Clinical Pharmacology (12.3)]*.

14 CLINICAL STUDIES

14.1 Pulmonary Arterial Hypertension (WHO Group 1)

TRIUMPH I was a 12-week, randomized, double-blind, placebo-controlled multi-center study of patients with PAH. The study population included 235 clinically stable patients with pulmonary arterial hypertension (WHO Group 1), nearly all with NYHA Class III (98%) symptoms who were receiving either bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase-5 inhibitor) for at least three months prior to study initiation. Concomitant therapy also could have included anticoagulants, other vasodilators (e.g., calcium channel blockers), diuretics, oxygen, and digitalis, but not a prostacyclin. These patients were administered either placebo or treprostinil inhalation solution in four daily treatment sessions with a target dose of 9 breaths (equivalent to 79.5 mcg YUTREPIA) per session over the course of the 12-week study. Patients were predominantly female (82%), had the origin of PAH as idiopathic/heritable (56%), secondary to connective tissue diseases (33%) or secondary to HIV or previous use of anorexigens (12%); bosentan was the concomitant oral medication in 70% of those enrolled, sildenafil in 30%.

The primary efficacy endpoint of the trial was the change in six-minute walk distance (6MWD) relative to baseline at 12 weeks. 6MWD was measured at peak exposure (between 10 and 60 minutes after dosing), and 3-5 hours after bosentan or 0.5-2 hours after sildenafil. Patients receiving treprostinil inhalation solution had a placebo-corrected median change from baseline in peak 6MWD of 20 meters at Week 12 ($p<0.001$).

The distribution of these 6MWD changes from baseline at Week 12 were plotted across the range of observed values (Figure 1). 6MWD measured at trough exposure (defined as measurement of 6MWD at least 4 hours after dosing) improved by 14 meters. There were no placebo-controlled 6MWD assessments made after 12 weeks.

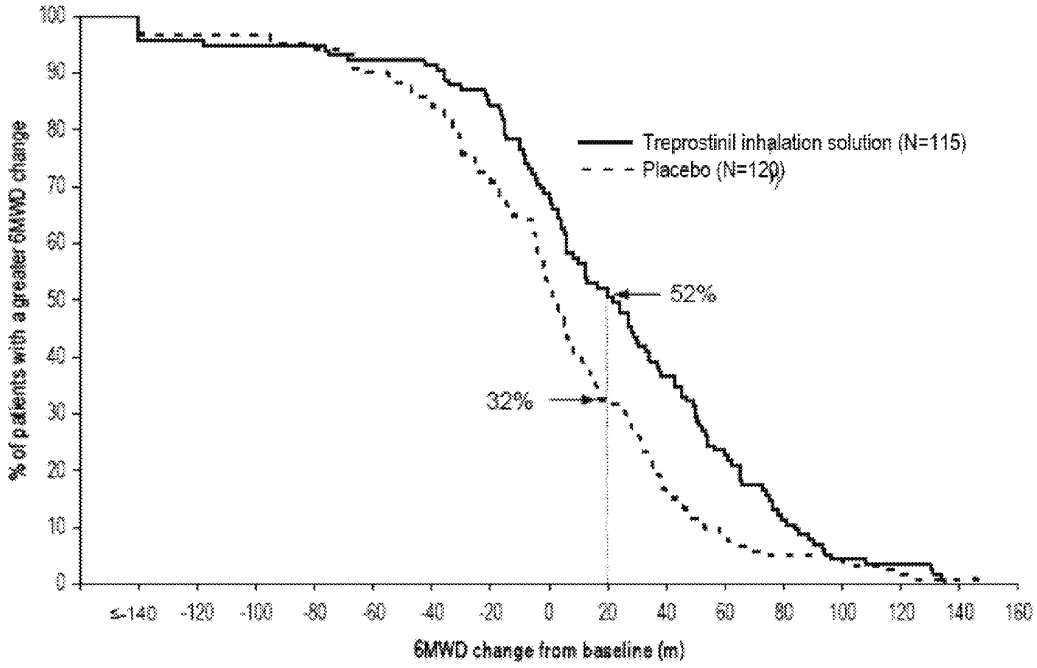


Figure 1. Distributions of 6MWD Changes from Baseline at Week 12 during Peak Plasma Concentration of Treprostinil Inhalation Solution

The placebo-corrected median treatment effect on 6MWD was estimated (using the Hodges-Lehmann estimator) within various subpopulations defined by age quartile, gender, geographic region of the study site, disease etiology, baseline 6MWD quartile, and type of background therapy (Figure 2).

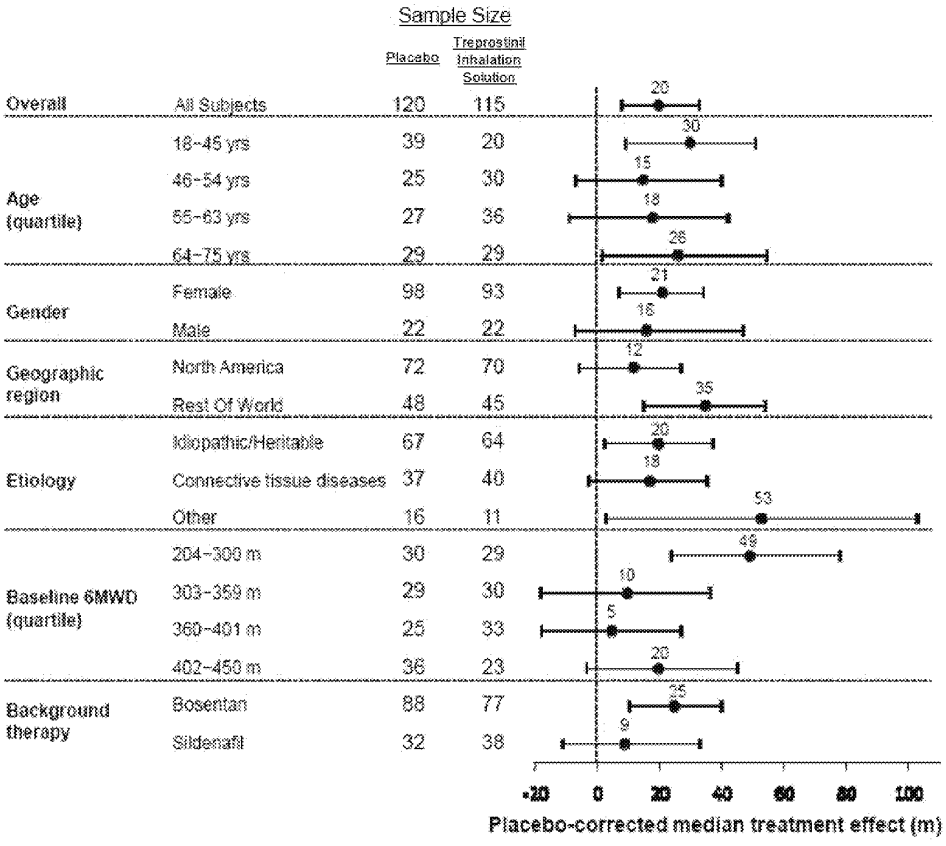


Figure 2. Placebo-Corrected Median Treatment Effect (Hodges-Lehmann estimate with 95% CI) on 6MWD Change from Baseline at Week 12 During Peak Plasma Concentration of Treprostinil Inhalation Solution for Various Subgroups

16 HOW SUPPLIED/STORAGE AND HANDLING

YUTREPIA is supplied in a carton consisting of 1 capsule based, dry powder inhaler (referred to as "inhaler"), 28 capsules (7 foil blister cards of 4 capsules each), and 7 single-use cleaning brushes. The individual capsule well is connected by an air channel to a separate blister well containing a desiccant strip. Descriptions of YUTREPIA carton by capsule strength are provided in Table 3 below:

Table 3: YUTREPIA Carton Contents by Capsule Strength

Capsule Strength (mcg treprostinil)	Capsule Description	NDC Number
26.5	Opaque yellow cap, clear body, imprinted with "LIQUIDIA 26.5" in black ink radially on cap	72964-011-01
53	Opaque green cap, clear body, imprinted with "LIQUIDIA 53" in white ink radially on cap	72964-012-01
79.5	Opaque blue cap, clear body, imprinted with "LIQUIDIA 79.5" in white ink radially on cap	72964-013-01
106	Opaque purple cap, clear body, imprinted with "LIQUIDIA 106" in white ink radially on cap	72964-014-01

YUTREPIA inhalation powder capsules should only be delivered using the capsule-based inhaler.. The off-white plastic inhaler consists of a blue protective cap marked with YUTREPIA and a base with a mouthpiece, capsule chamber, and two blue push buttons. Discard the inhaler device after 7 days of use or 56 actuations, whichever comes first.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Capsules should remain in the blister to protect them from moisture and light, and each capsule should be removed only when ready to administer a dose.

Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Instructions for Use).

Train patients in the administration process for YUTREPIA, including dosing, inhaler preparation, administration, cleaning, and maintenance, according to the instructions for use *[see Instructions for Use]*.

To avoid potential interruptions in drug delivery because of equipment malfunction, patients should have access to a back-up.

In the event that a scheduled dose is missed, take another dose as soon as possible.

Distributed by: Liquidia Technologies, Inc. Morrisville, NC 27560

Instructions for Use
YUTREPIA™ (you-TREP-ee-uh)
(trepostinil)
inhalation powder, for oral inhalation

This Instructions for Use contains information on how to inhale YUTREPIA™. Read these Instructions for Use before you start using YUTREPIA and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

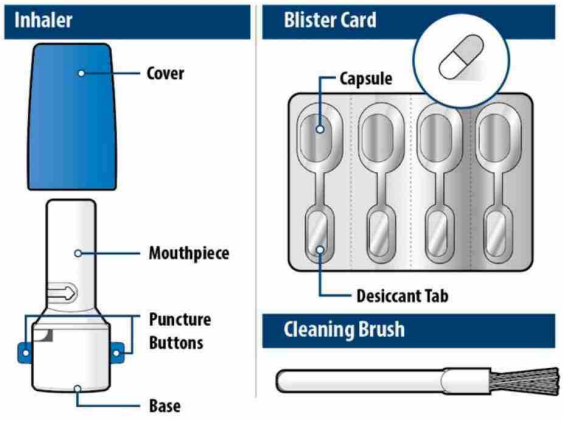
Your healthcare provider should show you or your caregiver how to use YUTREPIA the right way before you use it for the first time.

Important information you need to know before inhaling YUTREPIA inhalation powder:

- **Do not** swallow YUTREPIA capsules. YUTREPIA is for inhalation only.
- Use YUTREPIA as prescribed by your healthcare provider.
- YUTREPIA capsules come in 4 strengths: 26.5 mcg, 53 mcg, 79.5 mcg, and 106 mcg.
- If your prescribed dose is more than 106 mcg, you will need to inhale 2 YUTREPIA capsules. **See Figure C**: Dosing Chart to help you identify the 2 capsules needed for your prescribed dose. Only use the capsule combinations in the Dosing Chart when your prescribed dose is more than 106 mcg.
- **The capsule must be inhaled within 5 minutes of opening the blister card or the full dose may not be administered. Read through this instruction sheet prior to the first use of this product.**
- Always inhale each capsule 2 times to make sure you get your full dose of YUTREPIA.
- **Do not** wash the inhaler. Keep the inhaler dry.
- Wash and dry your hands your hands before using YUTREPIA.
- If the contents of the capsule comes in contact with your skin or eyes, rinse the area immediately with water.
- YUTREPIA capsules should remain in the blister card(s) and each capsule should be removed only when ready to deliver a dose.

Storing YUTREPIA

- Store YUTREPIA carton in a clean, dry place at room temperature between 68°F to 77°F (20°C to 25°C).
- Leave YUTREPIA capsules in blister card to protect from moisture and light.
- Throw away the inhaler after 7 days of use or 56 capsules whichever comes first.
- **Keep YUTREPIA and all medicines out of the reach of children.**

Text	Illustration
Get to know YUTREPIA	
The YUTREPIA carton contains (See Figure A): • 1 dry powder inhaler (called "inhaler" in these instructions) • 7 Foil blister cards of YUTREPIA capsules (called "capsules" in these instructions) containing 4 capsules each, in one of 4 available strengths • 7 Cleaning brushes (1 for each day) • 1 Desiccant tab within each blister strip to keep the capsule dry and prevent moisture. Throw away the blister strip and the desiccant tab after removing the capsule.	 **Figure A**

Preparing to use YUTREPIA

The capsule must be inhaled within 5 minutes of opening the blister card. Ensure all supplies are gathered and you are familiar with the use of the product prior to opening the card.

STEP 1. Gather your supplies.

a. Place your YUTREPIA carton on a clean, dry surface.
b. Remove the inhaler and foil blister cards from the carton **(See Figure B)**.

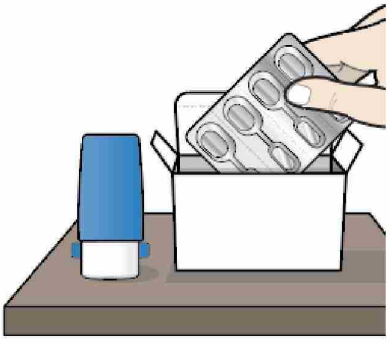


Figure B

STEP 2. Select the capsule(s) for your dose.

Use the Dosing Chart **(See Figure C)** to help you identify the capsule(s) needed for your prescribed dose.

- If your prescribed dose is more than 106 mcg, you will need to inhale 2 capsules per the table above.
- Only load and inhale 1 capsule at a time.
- All capsules in a carton are the same strength. If your prescribed dose requires 2 capsules of different strengths, you will need to select your capsules from 2 separate cartons.

IMPORTANT: For doses requiring 2 capsules, only use the capsule combinations presented in the Dosing Chart above **(See Figure C)**. The order for inhaling 2 capsules does not matter, regardless of capsule strength.

		Capsules Needed
Dose (mcg)	26.5	1 Yellow (26.5 mcg)
	53	1 Green (53 mcg)
	79.5	1 Blue (79.5 mcg)
	106	1 Purple (106 mcg)
	132.5	1 Green (53 mcg) + 1 Blue (79.5 mcg)
	159	2 Blue (79.5 mcg)
	185.5	1 Blue (79.5 mcg) + 1 Purple (106 mcg)
	212	2 Purple (106 mcg)

Figure C

STEP 3. Check the inhaler and blister card(s).

a. Look at the inhaler and blister card(s) to make sure they are not damaged **(See Figure D)**.
Do not use the inhaler or capsules if they are damaged.

b. Look at the expiration date on the blister cards to make sure it has not passed **(See Figure E).**
Do not use the capsules if the expiration date has passed.

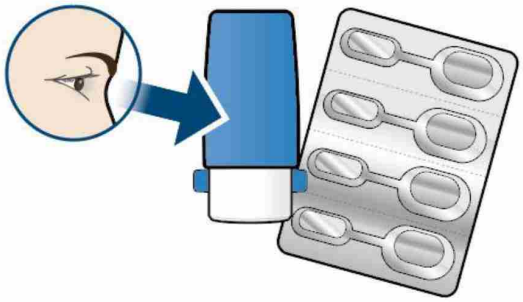


Figure D

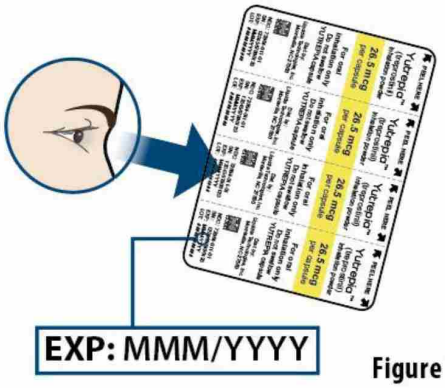


Figure E

Loading YUTREPIA

STEP 4. Open the inhaler.

a. Pull the cover straight off the inhaler **(See Figure F).**

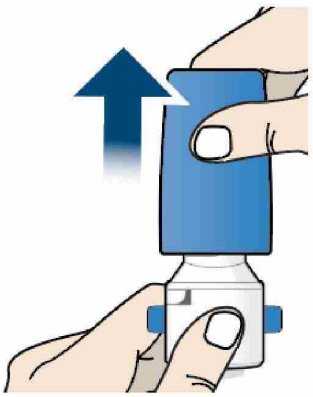
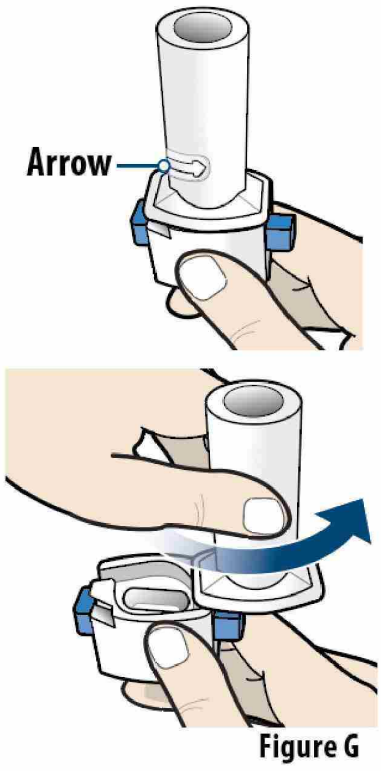
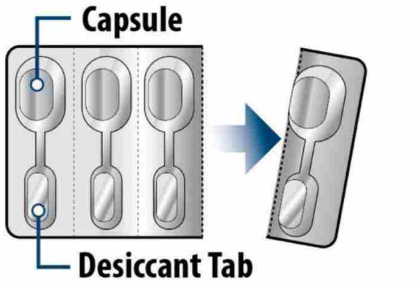
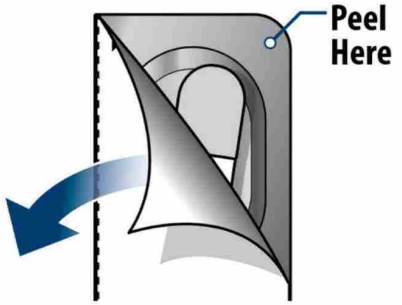
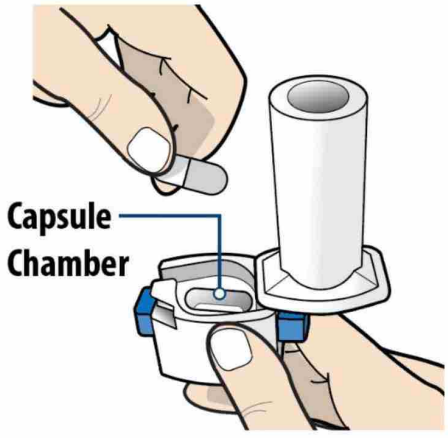
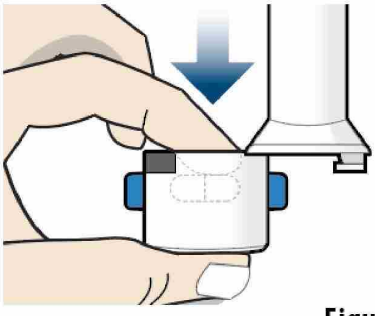
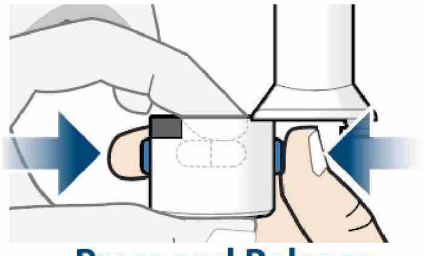


Figure F

b. Rotate the mouthpiece in the direction of the arrow (counter-clockwise) to open the inhaler and expose the capsule chamber **(See Figure G)**. If the mouthpiece separates from the base of the inhaler, gently reattach the 2 pieces and continue to follow the instructions.	 Figure G
STEP 5. Remove the capsule from the blister strip. a. Separate 1 blister strip by tearing at the pre-cut lines **(See Figure H)**. **Do not** remove a capsule from the blister strip until you are ready to deliver your dose. b. Peel the foil away from the blister strip, remove the capsule **(See Figure I)**. **Do not** swallow the capsule. **Do not** push the capsule through the foil. **Do not** remove the desiccant tab. **Capsule** must be used **within 5 minutes** of opening the blister card.	 Figure H  Figure I

STEP 6. Secure the capsule in the inhaler. a. Hold the inhaler in an upright position. b. Place the capsule in the capsule chamber in the base of the inhaler **(See Figure J)**. Only load 1 capsule. **Do not** place a capsule in the mouthpiece. **Do not** swallow capsules.	 Figure J
STEP 7. Puncture the capsule. a. Put one finger on top of the capsule to hold it down **(See Figure K)**. b. While still holding down the capsule, firmly press both puncture buttons all the way in with your other hand **(See Figure L).** Then let go of (release) the puncture buttons. This will puncture the capsule. You only need to press the puncture buttons 1 time. c. Hold the base of the inhaler and rotate the mouthpiece to close it.	 Figure K  Figure L

Inhaling YUTREPIA

STEP 8. Position the inhaler.
Hold the inhaler upright and away from your mouth. **(See Figure M)**.
Do not hold the inhaler by the puncture buttons.

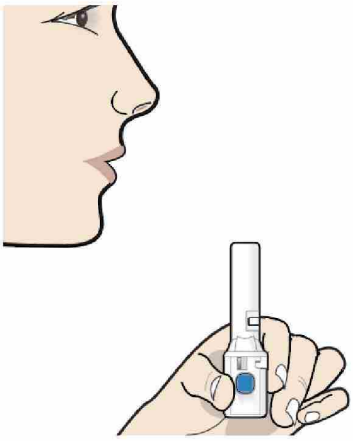


Figure M

STEP 9. Breathe out (exhale).
Breathe out fully and away from the inhaler **(See Figure N)**.
Do not exhale into the mouthpiece.

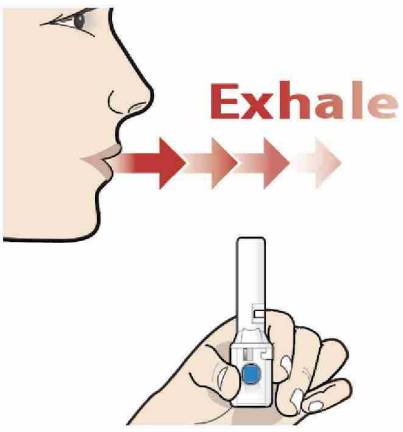


Figure N

STEP 10. Breathe in deeply (inhale)

a. Close your lips around the mouthpiece **(See Figure O)**.
b. Tilt your head back slightly **(See Figure O)**.
c. Take a comfortable deep breath in (inhale) until your lungs feel full **(See Figure O)**.
As you inhale, you will hear or feel a whirring noise as the capsule spins and releases medicine.

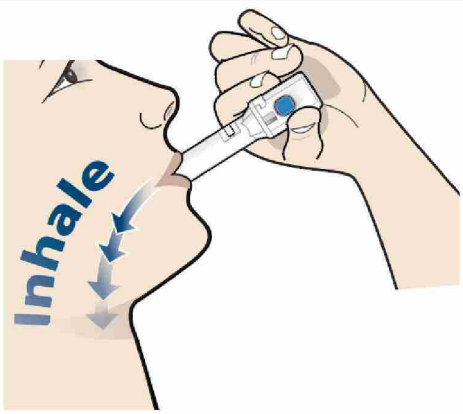


Figure O

STEP 11. Hold breath, then breathe out (exhale). a. Take the inhaler out of your mouth and hold your breath for 5 seconds or as long as you comfortably can **(See Figure P)**. b. Then breathe out normally. **IMPORTANT:** If you cough when inhaling, repeat STEP 8 through11.	 Figure P
STEP 12. Inhale again. To make sure the capsule is completely emptied of medicine, repeat STEP 8 through11 **(See Figure Q)**. Always inhale each capsule 2 times to make sure you get your full dose.	 Figure Q

Removing and disposing of the capsule

STEP 13. Open the inhaler.

a. Rotate the mouthpiece in the direction of the arrow (counter-clockwise) to open the inhaler and expose the capsule chamber **(See Figure R)**.
b. Remove the used (empty) capsule and throw away (dispose of) into household trash **(See Figure S)**.
c. See box below if you need to use more than 1 capsule to complete your prescribed dose.
d. Continue to Step 14 if you have completed your prescribed dose.

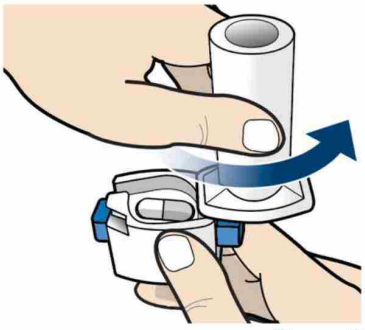


Figure R

Figure S

When dosing with more than one capsule (for doses 132.5 mcg and larger)

If you need to use more than one capsule to complete your prescribed dose, repeat STEP 4 through 13 with each additional capsule.

The order for dosing the capsules does not matter, regardless of capsule strength.

Closing and storing the inhaler

STEP 14. Close the inhaler.

a. Hold the base of the inhaler and rotate the mouthpiece to close it **(See Figure T).**
b. Put the cover on the inhaler **(See Figure U)**.
c. Store the inhaler in a clean, dry place at room temperature.

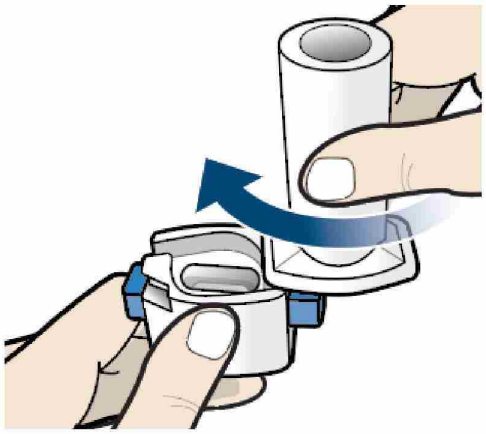


Figure T

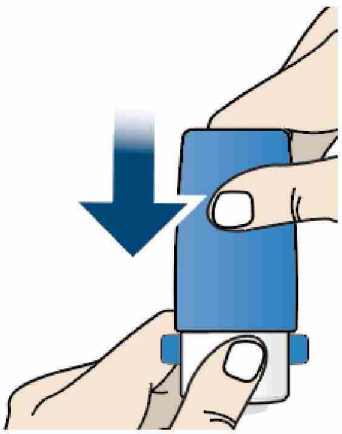


Figure U

Cleaning the inhaler (at end of each day)

Clean the outside and inside of the inhaler after your last dose of the day.

a. Wipe the mouthpiece with a dry paper towel, tissue, or clean dry cloth **(See Figure V)**.

b. Use the cleaning brush provided to clean the capsule chamber in order to remove visible powder buildup **(See Figure W)**.
NOTE: Throw away the brush after cleaning. Use only 1 brush each day.

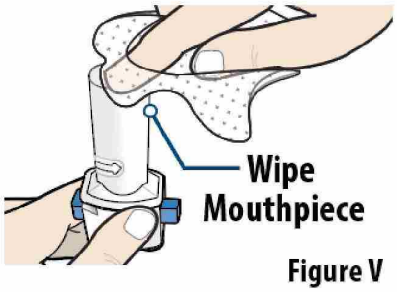


Figure V

Figure W

Disposing of the inhaler

Throw away (dispose of) the inhaler into household trash after 7 days of use.

The inhaler is reusable and will last for 7 days (1 week) or 56 capsules, whichever comes first.
(See Figure X).

Figure X

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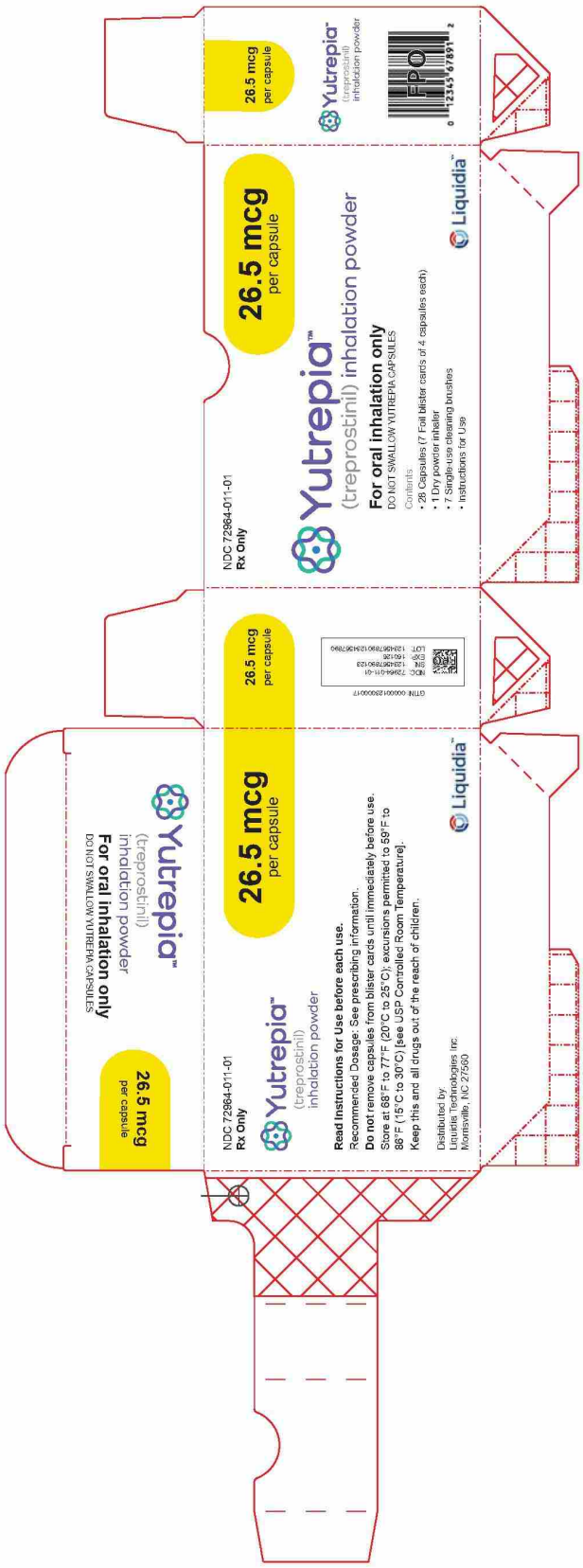
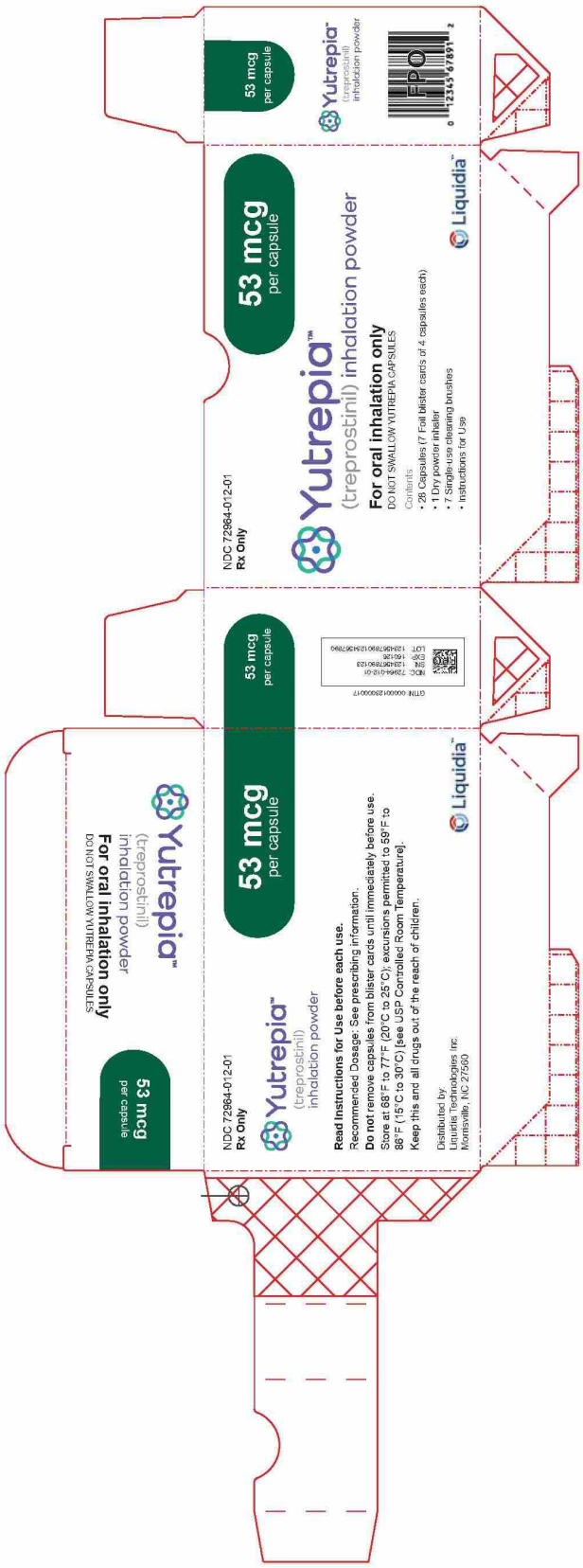
For more information call 1-800-###-#### or go to www.YUTREPIA.com

This Instructions for Use has been approved by the U.S. Food and Drug Administration

Issued: November 2021


26.5 mcg
per capsule
Yutrepia™
(treprostinil)
inhalation powder
For oral inhalation only
DO NOT SWALLOW YUTREPIA CAPSULES
NDC 72964-011-01
Rx Only
Liquidia™
Read Instructions for Use before each use.
Recommended Dosage: See prescribing information.
Do not remove capsules from blister cards until immediately before use.
Store at 68°F to 77°F (20°C to 25°C); excursions permitted to 59°F to 86°F (15°C to 30°C) [see USP Controlled Room Temperature].
Keep this and all drugs out of the reach of children.
Distributed by:
Liquidia Technologies, Inc.
Morrisville, NC 27560
Contents:
• 28 Capsules (7 Foil blister cards of 4 capsules each)
• 1 Dry powder inhaler
• 7 Single-use cleaning brushes
• Instructions for Use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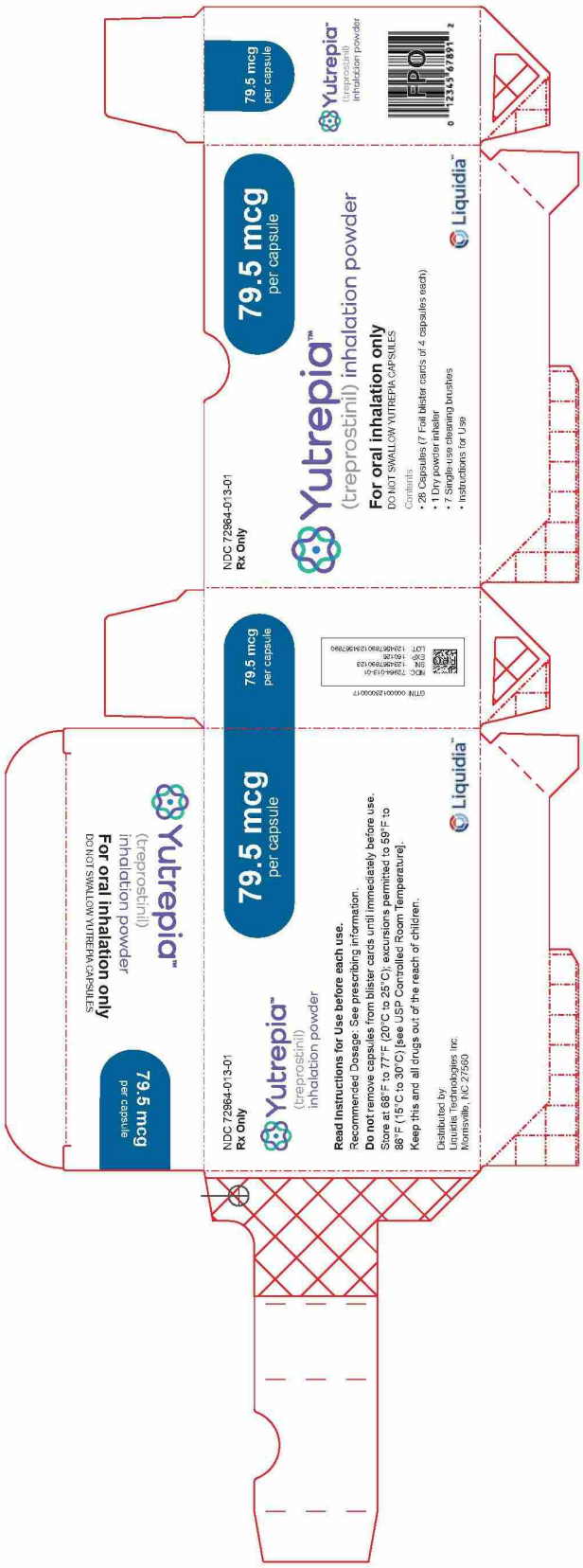
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Rx Only
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PEEL HERE
Yutrepia™
(treprostinil)
inhalation powder
26.5 mcg
per capsule
For oral
inhalation only
Do not swallow
YUTREPIA capsule
Dist. by:
Liquidia Technologies, Inc.
Morrisville, NC 27560
FPO
NDC: 72964-011-01
EXP: MMM/YYYY
LOT: ##########

PEEL HERE
Yutrepia™
(treprostinil)
inhalation powder
53 mcg
per capsule
For oral
inhalation only
Do not swallow
YUTREPIA capsule
Dist. by:
Liquidia Technologies, Inc.
Morrisville, NC 27560
FPO
0 12345 67891 2
NDC: 72964-012-01
EXP: MMM/YYYY
LOT: ##########

PEEL HERE
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0 12345 67891 2
NDC: 72964-014-01
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LOT: ##########

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